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L4: Entry 30 of 149 File: USPT Jul 25, 2000

DOCUMENT-IDENTIFIER: US 6093797 A
TITLE: Tri-, Tetra-, Penta-, and polypeptides and their therapeutic use as an antidepressant agent

Drawing Description Text (54):
In another embodiment of the invention, additional tripeptides are characterized by replacement of Leu with Arg or D-Arg; replacement of Gly with Ala; optional replacement of Pro with dehydro-Pro, preferably 3,4-dehydro-Pro; optional modification of the C-terminus amide group with a functional group selected from the group of a carboxyl group, a hydroxyalkyl group, preferably a hydroxymethyl group, an alkoxycarbonyl group, or an alkylated carbamyl group; optional modification of the N-terminus heterocyclic nitrogen ring of Pro.sup.1 with a substituent selected from the group of a lower alkyl group, preferably having 1 to 3 carbon atoms, a halogen atom, preferably a fluorine or chlorine atom, a hydroxyl group, preferably a cis- or trans-4-OH- group, a sulphydryl group, preferably a cis- or trans-4-thio- group; or an alkylamino group or a dialkylamino group, preferably a methyl or ethyl amino or dimethyl or diethyl amino group; and/or optional modification of the hydrogen atoms at the nitrogen atoms of the amino acid peptide bonds with a lower alkyl group, preferably having 1 to 3 carbon atoms.

Drawing Description Text (63):
In a further embodiment according to the invention, the small tripeptides are characterized by replacement of Leu with Orn; replacement of Gly with Tyr; optional replacement of Pro with dehydro-Pro, preferably 3,4-dehydro-Pro; optional modification of the C-terminus amide group with a substituent selected from the group of a carboxyl group, a hydroxyalkyl group, preferably hydroxymethyl, an alkoxycarbonyl group, or an alkylated carbamyl group; optional modification of the N-terminus heterocyclic nitrogen ring of Pro.sup.1 with a substituent selected from the group of a lower alkyl group, preferably having 1 to 3 carbon atoms, a halogen atom, preferably a fluorine or chlorine atom, a hydroxyl group, preferably a cis- or trans-4-OH- group, a sulphydryl group, preferably a cis- or trans-4-thio- group, or an alkylamino group or a dialkylamino group, preferably a methyl or ethylamino or a dimethyl or diethylamino group; and/or optional modification of the hydrogen atoms at the nitrogen atoms of the amino acid peptide bonds with a lower alkyl group, preferably having 1 to 3 carbon atoms.

Drawing Description Text (72):
In yet another embodiment according to the invention, the small peptides are tetrapeptides characterized by either addition of a C-terminus amino acid of Trp or Tyr to Gly or addition of a N-terminus amino acid of Trp or Phe to Pro to the tripeptides having the MIF core sequence; optional replacement of Leu with Ile, Arg, D-Arg, or Trp; optional replacement of Pro with dehydro-Pro, preferably 3,4-dehydro-Pro; optional modification of the C-terminus amide with a substituent selected from the group of a carboxyl group, a hydroxyalkyl group, preferably a hydroxymethyl group, an alkoxycarbonyl group, or an alkylated carbamyl group; optional modification of the heterocyclic nitrogen rings of Pro.sup.1 and Trp and optional modification of the aromatic ring of Phe with a substituent selected from the group of a lower alkyl group, preferably having 1 to 3 carbon atoms, a halogen atom, preferably a fluorine or chlorine atom, a hydroxyl group, preferably a cis- or trans-4-OH- group, a sulphydryl group, preferably a cis- or trans-4-thio- group, or an alkylamino or a dialkylamino group, preferably a methyl or ethylamino or a dimethyl or diethylamino group; and/or optional modification of the hydrogen atoms at the nitrogen atoms of the amino acid peptide bonds with a lower alkyl group, preferably having 1 to 3 carbon atoms.

Drawing Description Text (116):

In yet another embodiment of the invention, the peptides are pentapeptides with either addition of two N-terminus amino acids of Phe, Tyr, Leu, or Ile to Pro.sup.1, addition of a N-terminus amino acid of Phe or Tyr to Pro.sup.1 and a C-terminus amino acid addition of Trp to Gly, or addition of a C-terminus amino acids of Trp to Gly and an internal amino acid between Pro.sup.1 and Gly, to tripeptides having the MIF core sequence; optional replacement of Leu with Ile or Trp: optional replacement of Pro with dehydro-Pro, preferably 3,4-dehydro-Pro; optional modification of the C-terminus amide with a substituent selected from the group of a carboxyl group, a hydroxyalkyl group, preferably a hydroxymethyl group, an alkoxycarbonyl group, or an alkylated carbamyl group; optional modification of the heterocyclic nitrogen ring of Pro.sup.1 and optional modification of the aromatic rings of Tyr or Phe with a substituent selected from the group of a lower alkyl group, preferably having 1 to 3 carbon atoms, a halogen atom, preferably a fluorine or chlorine atom, a hydroxyl group, preferably a cis- or trans-4-OH- group, a sulphydryl group, preferably a cis- or trans-4-thio- group, or an alkylamino or a dialkylamino group, preferably a methyl or ethylamino or a dimethyl or diethylamino group; and/or optional modification of the hydrogen atoms at the nitrogen atoms of the amino acid peptide bonds with a lower alkyl group, preferably having 1 to 3 carbon atoms.

Detailed Description Paragraph Table (11):
- - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:1 (D) OTHER INFORMATION:/lab - #el= 4F-Phe /note= - #"Phe residue modified at C4 with a fluorine - #atom." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:2 (D) OTHER INFORMATION:/lab - #el= 4Hyp /note= - #"Amino acid #2 is either cis- or trans- - #4Hyp." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:3 (D) OTHER INFORMATION:/lab - #el= D-Leu /note= - #"Amino acid #3 is D-Leu." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:5 (D) OTHER INFORMATION:/lab - #el= Trp-NH2 /note= - #"A modified Trp residue: an amine group replace - #s a hydroxyl - #group at the carboxy terminus." - - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: - # 78: - - Xaa Xaa Xaa Gly Xaa 1 - # 5 - - - - (2) INFORMATION FOR SEQ ID NO: 79: - - (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 5 amino - #acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear - - (ii) MOLECULE TYPE: peptide - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:1 (D) OTHER INFORMATION:/lab - #el= 4F-Phe /note= - #"Phe residue modified at C4 with a fluorine - #atom." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:2 (D) OTHER INFORMATION:/lab - #el= 3Hyp /note= - #"Amino acid #2 is trans-3-hydroxy-Pro." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:5 (D) OTHER INFORMATION:/lab - #el= Trp-NH2 /note= - #"A modified Trp residue: an amine group replace - #s a hydroxyl - #group at the carboxy terminus." - - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: - # 79: - - Xaa Xaa Arg Gly Xaa 1 - # 5 - - - - (2) INFORMATION FOR SEQ ID NO: 80: - - (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 6 amino - #acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear - - (ii) MOLECULE TYPE: peptide - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:1 (D) OTHER INFORMATION:/lab - #el= 4F-Phe /note= - #"Phe residue modified at C4 with a fluorine - #atom." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:2 (D) OTHER INFORMATION:/lab - #el= 3-4DeH-Pro /note= - #"Proline residue with C3=C4 double bond." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:6 (D) OTHER INFORMATION:/lab - #el= Trp-NH2 /note= - #"A modified Trp residue: an amine group replace - #s a hydroxyl - #group at the carboxy terminus." - - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: - # 80: - - Xaa Xaa Arg Gly Gly Xaa 1 - # 5 - - - - (2) INFORMATION FOR SEQ ID NO: 81: - - (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 5 amino - #acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear - - (ii) MOLECULE TYPE: peptide - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:1 (D) OTHER INFORMATION:/lab - #el= 4CH3O-Phe /note= - #"Phe residue modified at C4 with a methoxy g - #roup." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:2 (D) OTHER INFORMATION:/lab - #el= 3-4DeH-Pro /note= - #"Proline residue with a C3=C4 double bond." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:5 (D) OTHER INFORMATION:/lab - #el= Trp-NH2 /note= - #"A modified Trp residue: an amine group replace - #s a hydroxyl - #group at the carboxy terminus." - - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: - # 81: - - Xaa Xaa Arg Gly Xaa 1 - # 5 - - - - (2) INFORMATION FOR SEQ ID NO: 82: - - (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 5 amino - #acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear - - (ii) MOLECULE TYPE: peptide - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:1 (D) OTHER INFORMATION:/lab - #el= 2-4DiF-Phe /note= - #"Phe residue modified at C2 and C4 with a - #fluorine atom." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:2 (D) OTHER INFORMATION:/lab - #el= 3-4DiH-Pro /note= - #"A modified proline residue: a double bond is replace w - #ith a hydrogen atom at each of C3 and C4." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:5 (D) OTHER INFORMATION:/lab - #el= Trp-NH2 /note= - #"A modified Trp residue: an amine group replace - #s a hydroxyl - #group at the carboxy terminus." - - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: - # 82: -

- Xaa Xaa Arg Gly Xaa 1 - # 5 - - - - (2) INFORMATION FOR SEQ ID NO: 83: - - (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 5 amino - #acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear - - (ii) MOLECULE TYPE: peptide - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:1 (D) OTHER INFORMATION:/lab - #el= 4-CF3-Phe /note= - #"Phe residue modified at C4 with a trifluoro methyl gr - #oup." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:2 (D) OTHER INFORMATION:/lab - #el= 3-4DeH-Pro /note= - #"Proline residue with C3=C4 double bond." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:5 (D) OTHER INFORMATION:/lab - #el= Trp-NH2 /note= - #"A modified Trp residue: an amine group replace - #s a hydroxyl - #group at the carboxy terminus." - - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: - #83: - - Xaa Xaa Arg Gly Xaa 1 - # 5 - - - - (2) INFORMATION FOR SEQ ID NO: 84: - - (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 5 amino - #acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear - - (ii) MOLECULE TYPE: peptide - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:1 (C) OTHER INFORMATION:/lab - #el= 4F-PhenylGly /note= - #"A Gly residue modified at the N-terminus with - #a phenyl gr - #oup having a fluorine atom at C4. - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:2 (D) OTHER INFORMATION:/lab - #el= 3-4DeH-Pro /note= - #"Proline residue with C3=C4 double bond." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:5 (D) OTHER INFORMATION:/lab - #el= Trp-NH2 /note= - #"A modified Trp residue: an amine group replace - #s a hydroxyl - #group at the carboxy terminus." - - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: - #84: - - Xaa Xaa Arg Gly Xaa 1 - # 5 - - - - (2) INFORMATION FOR SEQ ID NO: 85: - - (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 5 amino - #acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear - - (ii) MOLECULE TYPE: peptide - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:1 (D) OTHER INFORMATION:/lab - #el= 3F-Tyr /note= - #"Tyr residue modified at C3 with a fluorine - #atom." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:2 (D) OTHER INFORMATION:/lab - #el= 3-4DeH-Pro /note= - #"Proline residue with C3=C4 double bond." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:5 (D) OTHER INFORMATION:/lab - #el= Trp-NH2 /note= - #"A modified Trp residue: an amine group replace - #s a hydroxyl - #group at the carboxy terminus." - - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: - #85: - - Xaa Xaa Arg Gly Xaa 1 - # 5 - - - - (2) INFORMATION FOR SEQ ID NO: 86: - - (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 5 amino - #acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear - - (ii) MOLECULE TYPE: peptide - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:1 (D) OTHER INFORMATION:/lab - #el= 4F-Phe /note= - #"Phe residue modified at C4 with a fluorine - #atom." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:2 (D) OTHER INFORMATION:/lab - #el= 3-4DeH-Pro /note= - #"Proline residue with C3=C4 double bond." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:5 (D) OTHER INFORMATION:/lab - #el= Trp-NHOH /note= - #"A modified Trp residue: a hydroxyamino group replaces - #a hydroxyl group at the carboxy terminus." - - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: - #86:

Detailed Description Paragraph Table (15):
(B) LOCATION:4 (D) OTHER INFORMATION:/lab - #el= Gly-NH2 /note= "A modifi - #ed Gly residue: an amine group replaces a hydroxyl - #group at the carboxy terminus." - - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: - #112: - - Tyr Pro Leu Xaa 1 - - - - (2) INFORMATION FOR SEQ ID NO: 113: - - (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 4 amino - #acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear - - (ii) MOLECULE TYPE: peptide - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:1 (D) OTHER INFORMATION:/lab - #el= R1-AA1 /note= - #"A Trp, Tyr or Phe residue modified with a hydrogen - #atom; a lower alkyl group; a halogen atom; or - #a hydroxyl, - #sulphydryl, alkylamino or dialkylamino group." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:2 (D) OTHER INFORMATION:/lab - #el= R2-Pro1 /note= - #"A Pro or dehydro-Pro residue modified with a hydrogen - #atom; a lower alkyl group; a halogen atom; or - #a hydroxyl, - #sulphydryl, alkylamino or dialkylamino group." - - FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:3 (D) OTHER INFORMATION:/lab - #el= AA2 /note= - #"An amino acid of the group Leu, Ile and - #Trp." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:4 (D) OTHER INFORMATION:/lab - #el= Gly-R /note= - #"A Gly residue modified with a carboxyl group, a hydroxy - #alkyl group, a carbamyl group, an alkylcarbam yl group, or - # an alkoxycarbonyl group at the carboxy terminus." - - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: - #113: - - Xaa Xaa Xaa Xaa 1 - - - - (2) INFORMATION FOR SEQ ID NO: 114: - - (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 4 amino - #acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear - - (ii) MOLECULE TYPE: peptide - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:1 (D) OTHER INFORMATION:/lab - #el= R1-AA1 /note= - #"A Leu, Ile or Trp residue modified with a hydrogen atom; a lo - #wer alkyl group; a halogen; or a hydroxyl, sulphydryl, - #alkylamino, or dialkylamino group." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:2 (D) OTHER INFORMATION:/lab - #el= R2-Pro1 /note= - #"A Pro or dehydro-Pro residue modified with a hydrogen - #atom; a halogen

atom; or a lower alkyl, hydroxyl, - #sulphydryl, alkylamino, or dialkylamino group." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:3 (D) OTHER INFORMATION:/lab - #el= AA2 /note= - #"An amino acid of the group Leu, Ile, and - #Trp, with the - #proviso that AA2 cannot be Trp if the amino - #acid at locati - #on 1 is a Tyr residue modified with a hydrog - #en atom and - #the amino acid at location 2 is a Pro residu - #e modified - #with a hydrogen atom." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:4 (D) OTHER INFORMATION:/lab - #el= Gly-NH2 /note= - #"A modified Gly residue: an amine group replace - #s a hydroxyl - #group at the carboxy terminus." - - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: - #114: - - Xaa Xaa Xaa Xaa 1 - - - - (2)INFORMATION FOR SEQ ID NO: 115: - - (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 4 amino - #acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear - - (ii) MOLECULE TYPE: peptide - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:1 (D) OTHER INFORMATION:/lab - #el= R1-AA1 /note= - #"A Trp, Tyr or Phe residue modified with a hydrogen - #atom; a halogen atom; or a lower alkyl, hydroxyl, - #sulphydryl, alkylamino or dialkylamino group." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:2 (D) OTHER INFORMATION:/lab - #el= R2-Pro1 /note= - #""R2-Pro1 is a Pro or dehydro-Pro residue mo - #dified with a - #hydrogen atom; a halogen atom; or a lower alkyl - #, a hydroxyl, - #sulphydryl, alkylamino, or dialkylamino group, wherein t - #he N-terminus heterocyclic nitrogen ring of the Pro or - #dehydro-Pro residue is modified with a cis- or - #trans -4-OH- gr - #oup." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:3 (D) OTHER INFORMATION:/lab - #el= AA2 /note= - #"A amino acid of the group Leu, Ile, Trp - #and Ar (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:4 (D) OTHER INFORMATION:/lab - #el= Gly-R /note= - #"A Gly residue modified with a carboxyl, hydroxyalkyl - #, carbamyl, alkylcarbamyl or alkoxycarbony l group at - #the carboxy terminus." - - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: - #115: - - Xaa Xaa Xaa Xaa 1 - - - - (2) INFORMATION FOR SEQ ID NO: 116: - - (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 5 amino - #acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear - - (ii) MOLECULE TYPE: peptide - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:1 (D) OTHER INFORMATION:/lab - #el= R1-AA1 /note= - #"A Phe or Tyr residue modified with a hydrog - #en atom; a - #halogen atom; a lower alkyl, hydroxyl, sulphydryl, - #alkylamino, or dialkylamino group." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCN:2 (D) OTHER INFORMATION:/lab - #el= AA2 /note= - #"An amino acid from the group Phe and Tyr." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:3 (D) OTHER INFORMATION:/lab - #el= R2-Pro1 /note= "A - #Pro or dehydro-Pro residue modified with a hydrogen atom; - #a halogen atom; or a lower alkyl, hydroxyl, sulphydryl, alkyl - #amino or dialkylamino group." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:4 (D) OTHER INFORMATION:/lab - #el= AA3 /note= - #"An amino acid from the group of Leu and - #Ile." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:5 (D) OTHER INFORMATION:/lab - #el= Gly-R /note= - #"A Gly residue modified with a carboxyl, hydroxyalkyl - #, carbamyl, alkylcarbamyl or alkoxycarbony l group at - #the carboxy terminus." - - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: - #116: - - Xaa Xaa Xaa Xaa Xaa 1 - # 5 - - - - (2) INFORMATION FOR SEQ ID NO: 117: - - (i) SEQUENCE CHARACTERISTICS: (A) LEN 5 amino acid - #s (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear - - (ii) MOLECULE TYPE: peptide - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:1 (D) OTHER INFORMATION:/lab - #el= R1-AA1 /note= "A - #Phe or Tyr residue modified with a hydrogen atom; a haloge - #n atom; or a lower alkyl, hydroxyl, carbamyl, alkylcarbamyl, or - # alkoxycarbonyl group." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:2 (D) OTHER INFORMATION:/lab - #el= AA2 /note= - #"An amino acid from the group Phe and Tyr." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:3 (D) OTHER INFORMATION:/lab - #el= R2-Pro1 /note= "A - #Pro or dehydro-Pro residue modified with a hydrogen atom; - #a halogen atom; or a lower alkyl, hydroxyl, sulphydryl, alkyl - #amino or dialkylamino group." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:4 (D) OTHER INFORMATION:/lab - #el= AA3 /note= - #"An amino acid of the group Leu and Ile." - - (ix) FEAT (A) NAME/KEY: Modified-sit - #e (B) LOCATION:5 (D) OTHER INFORMATION:/lab - #el= Gly-NH2 /note= - #"A modified Gly residue: an amine group replace - #s a hydroxyl - #group at the carboxy terminus." - - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: - #117: - - Xaa Xaa Xaa Xaa Xaa 1 - # 5 - - - - (2) INFORMATION FOR SEQ ID NO: 118: - - (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 5 amino - #acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear - - (ii) MOLECULE TYPE: peptide - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:1 (D) OTHER INFORMATION:/lab - #el= R1-Pro1 /note= "- #A Pro or dehydro-Pro residue modified with a hydrogen atom - #; a halogen atom; or a lower alkyl, hydroxyl, sulphydryl, a - #lkylamino or dialkylamino group." - - (ix) FEATURE: (A) NAME/KEY: Modified-sit - #e (B) LOCATION:2 (D) OTHER INFORMATION:/lab - #el= AA1

peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:28: PhePheValLeu 15 (2) INFORMATION FOR SEQ ID NO:29: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 5 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:29: PheLysPheValLeu 15 (2) INFORMATION FOR SEQ ID NO:30: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 5 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:30: LysLeuValAlaPhe 15 (2) INFORMATION FOR SEQ ID NO:31: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 6 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (ix) FEATURE: (A) NAME/KEY: Modified site (B) LOCATION: 6 (D) OTHER INFORMATION: /note= Xaa is beta-alanyl (xi) SEQUENCE DESCRIPTION: SEQ ID NO:31: LysLeuValPhePheXaa 1 (2) INFORMATION FOR SEQ ID NO:32: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 5 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (ix) FEATURE: (A) NAME/KEY: Modified site (B) LOCATION: 5 (D) OTHER INFORMATION: /note= Xaa is D-alanyl (xi) SEQUENCE DESCRIPTION: SEQ ID NO:32: LeuValPhePheXaa 1 (2) INFORMATION FOR SEQ ID NO:33: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 5 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:33: LeuValAlaPheAla 15 (2) INFORMATION FOR SEQ ID NO:34: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 5 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (ix) FEATURE: (A) NAME/KEY: Modified-site (B) LOCATION: 5 (D) OTHER INFORMATION: /note=aminoethyldibenzofuranyl- proprionic acid modification (xi) SEQUENCE DESCRIPTION: SEQ ID NO:34: AspAspIleIleLeu 15 (2) INFORMATION FOR SEQ ID NO:35: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 5 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:35: AlaAlaAlaAlaAla 15 (2) INFORMATION FOR SEQ ID NO:36: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 35 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:36: HisAspSerGlyTyrGluValHisHisGlnLysLeuValPhePheAla 151015 GluAspValGlySerAsnLysGlyAlaIleIleGlyLeuMetValGly 202530 GlyValVal 35 (2) INFORMATION FOR SEQ ID NO:37: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 15 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:37: GluValHisHisGlnLysLeuValPhePheAlaGluAspValGly 151015 (2) INFORMATION FOR SEQ ID NO:38: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 35 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:38: AspAlaGluPheArgHisAspSerGlyTyrGluValHisHisGlnLys 151015 LeuValPhePheAlaGluAspValGlyIleIleGlyLeuMetValGly 202530 GlyValVal 35 (2) INFORMATION FOR SEQ ID NO:39: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 35 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:39: AspAlaGluPheArgHisAspSerGlyTyrGluValHisHisGlnAla 151015 GluAspValGlySerAsnLysGlyAlaIleIleGlyLeuMetValGly 202530 GlyValVal 35 (2) INFORMATION FOR SEQ ID NO:40: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 35 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:40: AspAlaGluPheArgGluValHisHisGlnLysLeuValPhePheAla 151015 GluAspValGlySerAsnLysGlyAlaIleIleGlyLeuMetValGly 202530 GlyValVal 35

Other Reference Publication (21):
Hilibich, Caroline et al. (1992) "Substitutions of Hydrophobic Amino Acids Reduce the Amyloidogenicity of Alzheimer's Disease .beta.A4 Peptides" J. Mol. Biol. 228: 460-473.

Other Reference Publication (28):
Klunk, William E. and Jay W. Pettegrew (1990) "Alzheimer's .beta.-Amyloid Protein Is Covalently Modified When Dissolved in Formic Acid" Journal of Neurochemistry 54(6): 2050-2054.

Other Reference Publication (32):
Miller, Brian T. et al. (1994) "Identification and Characterization of O-Biotinylated Hydroxy Amino Acid Residues in Peptides" Analytical Biochemistry 219: 240-248.

Other Reference Publication (33):
Orlando, Ron et al. (1992) "Covalent Modification of Alzheimer's Amyloid .beta.-Peptide in Formic Acid Solutions" Biochemical and Biophysical Research Communications 184(2): 686-691.

Other Reference Publication (38):
Shen, Chih-Lung et al. (1994) "Effect of Acid Predissolution on Fibril Size and Fibril

Flexibility of Synthetic .beta.-Amyloid Peptide" Biophysical Journal 67: 1238-1246.

Mol. Cell. Biol. 4:2072-2081; Wondisford et al. (1988) Mol. Endocrinol. 2:32-39; Tratschin et al. (1984) J. Virol. 51:611-619; and Flotte et al. (1993) J. Biol. Chem. 268:3781-3790).

Detailed Description Text (177):
The invention provides a method for treating a subject for a disorder associated with .beta.-amyloidosis, comprising administering to the subject a recombinant expression vector encoding a .beta.-amyloid peptide compound, the compound comprising an amino acid sequence having at least one amino acid deletion compared to .beta.AP.sub.1-39, such that the .beta.-amyloid peptide compound is synthesized in the subject and the subject is treated for a disorder associated with .beta.-amyloidosis. Preferably, the disorder is Alzheimer's disease. In one embodiment the recombinant expression vector directs expression of the peptide compound in neuronal cells. In another embodiment, the recombinant expression vector directs expression of the peptide compound in glial cells. In yet another embodiment, the recombinant expression vector directs expression of the peptide compound in fibroblast cells.

Detailed Description Text (178):
General methods for gene therapy are known in the art. See for example, U.S. Pat. No. 5,399,346 by Anderson et al. A biocompatible capsule for delivering genetic material is described in PCT Publication WO 95/05452 by Baetge et al. Methods for grafting genetically modified cells to treat central nervous system disorders are described in U.S. Pat. No. 5,082,670 and in PCT Publications WO 90/06757 and WO 93/10234, all by Gage et al. Isolation and/or genetic modification of multipotent neural stem cells or neuro-derived fetal cells are described in PCT Publications WO 94/02593 by Anderson et al., WO 94/16718 by Weiss et al., and WO 94/23754 by Major et al. Fibroblasts transduced with genetic material are described in PCT Publication WO 89/02468 by Mulligan et al. Adenovirus vectors for transfering genetic material into cells of the central nervous system are described in PCT Publication WO 94/08026 by Kahn et al. Herpes simplex virus vectors suitable for treating neural disorders are described in PCT Publications WO 94/04695 by Kaplitt and WO 90/09441 by Geller et al. Promoter elements of the glial fibrillary acidic protein that can confer astrocyte specific expression on a linked gene or gene fragment, and which thus can be used for expression of A.beta. peptides specifically in astrocytes, is described in PCT Publication WO 93/07280 by Brenner et al. Furthermore, alternative to expression of an A.beta. peptide to modulate amyloidosis, an antisense oligonucleotide that is complementary to a region of the .beta.-amyloid precursor protein mRNA corresponding to the peptides described herein can be expressed in a subject to modulate amyloidosis. General methods for expressing antisense oligonucleotides to modulate nervous system disorders are described in PCT Publication WO 95/09236.

Detailed Description Text (179):
Alternative to delivery by gene therapy, a peptide compound of the invention comprising an amino acid sequence having at least one amino acid deletion compared to .beta.AP.sub.1-39 can be delivered to a subject by directly administering the peptide compound to the subject as described further herein for the modified peptide compounds of the invention. The peptide compound can be formulated into a pharmaceutical composition comprising a therapeutically effective amount of the .beta.-amyloid peptide compound and a pharmaceutically acceptable carrier. The peptide compound can be contacted with natural .beta.-amyloid peptides with a .beta.-amyloid peptide compound such that aggregation of the natural .beta.-amyloid peptides is inhibited. Moreover, the peptide compound can be administered to the subject in a therapeutically effective amount such that the subject is treated for a disorder associated with .beta.-amyloidosis, such as Alzheimer's disease.

Detailed Description Text (183):
Different amyloids are characterized by the type of protein(s) or peptide(s) present in the deposit. For example, as described hereinbefore, amyloid deposits associated with Alzheimer's disease comprise the .beta.-amyloid peptide and thus a modulator compound of the invention for detecting and/or treating Alzheimer's disease is designed based on modification of the .beta.-amyloid peptide. The identities of the protein(s) or peptide(s) present in amyloid deposits associated with a number of other amyloidogenic diseases have been elucidated. Accordingly, modulator compounds for use in the detection and/or treatment of these other amyloidogenic diseases can be prepared in a similar fashion to that described herein for .beta.-AP-derived modulators. In vitro assay systems can be established using an amyloidogenic protein or peptide which forms fibrils in vitro, analogous to the A.beta. assays described herein. Modulators can be identified using such assay systems, based on the ability of the modulator to disrupt the .beta.-sheet structure of the fibrils. Initially, an entire amyloidogenic protein

can be modified or, more preferably, a peptide fragment thereof that is known to form fibrils in vitro can be modified (e.g., analogous to A.beta.1-40 described herein). Amino acid deletion and substitution analyses can then be performed on the modified protein or peptide (analogous to the studies described in the Examples) to delineate an aggregation core domain that is sufficient, when modified, to disrupt fibril formation.

Detailed Description Text (187):
Islet Amyloid Polypeptide (IAPP, also known as amylin)--Amyloids containing IAPP occur in adult onset diabetes and insulinoma. IAPP is a 37 amino acid polypeptide formed from an 89 amino acid precursor protein (see e.g., Betsholtz, C., et al. (1989) Exp. Cell. Res. 183:484-493; Westermark, P., et al. (1987) Proc. Natl. Acad. Sci. USA 84:3881-3885). A peptide corresponding to IAPP residues 20-29 has been reported to form amyloid-like fibrils in vitro, with residues 25-29, having the sequence Ala-Ile-Leu-Ser-Ser (SEQ ID NO:18), being strongly amyloidogenic (Westermark, P., et al. (1990) Proc. Natl. Acad. Sci. USA 87:5036-5040; Glenner, G. G., et al. (1988) Biochem. Biophys. Res. Commun. 155:608-614). A peptide fragment of IAPP that forms amyloid fibrils can be modified as described herein to create a modulator of amyloidosis that can be used in the detection or treatment of adult onset diabetes or insulinoma.

Detailed Description Text (188):
Atrial Natriuretic Factor (ANF)--Amyloids containing ANF are associated with isolated atrial amyloid (see e.g., Johansson, B., et al. (1987) Biochem. Biophys. Res. Commun. 148:1087-1092). ANF corresponds to amino acid residues 99-126 (proANF99-126) of the ANF prohormone (proANP1-126) (Pucci, A., et al. (1991) J. Pathol. 165:235-241). ANF, or a fragment thereof, that forms amyloid fibrils can be modified as described herein to create a modulator of amyloidosis that can be used in the detection or treatment of isolated atrial amyloid.

Detailed Description Text (189):
Kappa or Lambda Light Chain--Amyloids containing kappa or lambda light chains are associated idiopathic (primary) amyloidosis, myeloma or macroglobulinemia-associated amyloidosis, and primary localized cutaneous nodular amyloidosis associated with Sjogren's syndrome. The structure of amyloidogenic kappa and lambda light chains, including amino acid sequence analysis, has been characterized (see e.g., Buxbaum, J. N., et al. (1990) Ann. Intern. Med. 112:455-464; Schormann, N., et al. (1995) Proc. Natl. Acad. Sci. USA 92:9490-9494; Hurle, M. R., et al. (1994) Proc. Natl. Acad. Sci. USA 91:5446-5450; Liepnieks, J. J., et al. (1990) Mol. Immunol. 27:481-485; Gertz, M. A., et al. (1985) Scand. J. Immunol. 22:245-250; Inazumi, T., et al. (1994) Dermatology 189:125-128). Kappa or lambda light chains, or a peptide fragment thereof that forms amyloid fibrils, can be modified as described herein to create a modulator of amyloidosis that can be used in the detection or treatment of idiopathic (primary) amyloidosis, myeloma or macroglobulinemia-associated amyloidosis or primary localized cutaneous nodular amyloidosis associated with Sjogren's syndrome.

Detailed Description Text (197):
Lysozyme--Amyloids containing a variant form of lysozyme have been found in hereditary systemic amyloidosis. In one family the disease was associated with a threonine to isoleucine mutation at position 56, whereas in another family the disease was associated with a histidine to aspartic acid mutation at position 67 (Pepys, M. B., et al. (1993) Nature 362:553-557). Lysozyme or a peptide fragment thereof that forms amyloid fibrils can be modified as described herein to create a modulator of amyloidosis that can be used in the detection or treatment of lysozyme-associated hereditary systemic amyloidosis.

Detailed Description Text (201):
A .beta.-amyloid modulator composed of an amino-terminally biotinylated .beta.-amyloid peptide of the amino acid sequence:

Detailed Description Text (202):
DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVV (positions 1 to 40 of SEQ ID NO:1) was prepared by solid-phase peptide synthesis using an N.sup..alpha. -9-fluorenylmethyloxycarbonyl (FMOC)-based protection strategy as follows. Starting with 2.5 mmoles of FMOC-Val-Wang resin, sequential additions of each amino acid were performed using a four-fold excess of protected amino acids, 1-hydroxybenzotriazole (HOBt) and diisopropyl carbodiimide (DIC). Recouplings were performed when necessary as determined by ninhydrin testing of the resin after coupling. Each synthesis cycle was minimally described by a three minute deprotection (25% piperidine/N-methyl-pyrrolidone

(NMP)), a 15 minute deprotection, five one minute NMP washes, a 60 minute coupling cycle, five NMP washes and a ninhydrin test. To a 700 mg portion of the fully assembled peptide-resin, biotin (obtained commercially from Molecular Probes, Inc.) was substituted for an FMOC-amino acid was coupled by the above protocol. The peptide was removed from the resin by treatment with trifluoroacetic acid (TFA) (82.5%), water (5%), thioanisole (5%), phenol (5%), ethanedithiol (2.5%) for two hours followed by precipitation of the peptide in cold ether. The solid was pelleted by centrifugation (2400 rpm.times.10 min.), and the ether decanted. It was resuspended in ether, pelleted and decanted a second time. The solid was dissolved in 10% acetic acid and lyophilized to dryness to yield 230 mg of crude biotinylated peptide. 60 mg of the solid was dissolved in 25% acetonitrile (ACN)/0.1% TFA and applied to a C18 reversed phase high performance liquid chromatography (HPLC) column. Biotinyl .beta.AP.sub.1-40 was eluted using a linear gradient of 30-45% acetonitrile/0.1% TFA over 40 minutes. One primary fraction (4 mg) and several side fractions were isolated. The main fraction yielded a mass spectrum of 4556 (matrix-assisted laser desorption ionization-time of flight) which matches the theoretical (4555) for this peptide.

Detailed Description Text (203):
A .beta.-amyloid modulator composed of an amino-terminally biotinylated .beta.-amyloid peptide of the amino acid sequence:

Detailed Description Text (204):
DAEFRHDSGYEVHHQ (positions 1 to 15 of SEQ ID NO:1) was prepared on an Advanced ChemTech Model 396 multiple peptide synthesizer using an automated protocol established by the manufacturer for 0.025 mmole scale synthesis. Double couplings were performed on all cycles using 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU)/N,N-diisopropylethylamine (DIEA)/HOBt/FMOC-AA in four-fold excess for 30 minutes followed by DIC/HOBt/FMOC-AA in four-fold excess for 45 minutes. The peptide was deprotected and removed from the resin by treatment with TFA/water (95%/5%) for three hours and precipitated with ether as described above. The pellet was resuspended in 10% acetic acid and lyophilized. The material was purified by a preparative HPLC using 15%-40% acetonitrile over 80 minutes on a Vydac C18 column (21.times.250 mm). The main isolate eluted as a single symmetrical peak when analyzed by analytical HPLC and yielded the expected molecular weight when analyzed by electrospray mass spectrometry. Result=2052.6 (2052 theoretical).

Detailed Description Text (205):
.beta.-amyloid modulator compounds comprising other regions of the .beta.-AP amino acid sequence (e.g., an A.beta. aggregation core domain) were similarly prepared using the synthesis methods described above. Moreover, modulators comprising other amyloidogenic peptides can be similarly prepared.

Detailed Description Text (227):
A series of N-terminally modified .beta.-amyloid peptides was synthesized using standard methods. Fully-protected resin-bound peptides corresponding to A.beta.(1-15) and A.beta.(1-40) were prepared as described in Example 1 on Wang resin to eventually afford carboxyl terminal peptide acids. Small portions of each peptide resin (13 and 20 .mu.moles, respectively) were aliquoted into the wells of the reaction block of an Advanced ChemTech Model 396 Multiple Peptide Synthesizer. The N-terminal FMOC protecting group of each sample was removed in the standard manner with 25% piperidine in NMP followed by extensive washing with NMP. The unprotected N-terminal .alpha.-amino group of each peptide-resin sample was modified using one of the following methods:

Detailed Description Text (228):
Method A, coupling of modifying reagents containing free carboxylic acid groups: The modifying reagent (five equivalents) was predissolved in NMP, DMSO or a mixture of these two solvents. HOBT and DIC (five equivalents of each reagent) were added to the dissolved modifier and the resulting solution was added to one equivalent of free-amino peptide-resin. Coupling was allowed to proceed overnight, followed by washing. If a ninhydrin test on a small sample of peptide-resin showed that coupling was not complete, the coupling was repeated using 1-hydroxy-7-azabenzotriazole (HOAt) in place of HOBt.

Detailed Description Text (231):
Method A was used to couple N-acetylneuraminic acid, cholic acid, trans-4-cotininecarboxylic acid, 2-imino-1-imidazolidineacetic acid, (S)-(-)-indoline-2-carboxylic acid, (-)-menthoxyacetic acid, 2-norbornaneacetic acid, .gamma.-oxo-5-acenaphthenebutyric acid, (-)-2-oxo-4-thiazolidinecarboxylic acid, and tetrahydro-3-furoic acid. Method B was used to couple

2-iminobiotin-N-hydroxysuccinimide ester, diethylenetriaminepentaacetic dianhydride, 4-morpholinecarbonyl chloride, 2-thiopheneacetyl chloride, and 2-thiophenesulfonyl chloride.

Detailed Description Text (234):
.beta.-amyloid modulator compounds comprising other regions of the .beta.-AP amino acid sequence (e.g., an A.beta. aggregation core domain) were similarly prepared using the synthesis methods described above. Moreover, modulators comprising other amyloidogenic peptides can be similarly prepared.

Detailed Description Text (262):
Effect of Different Amino Acid Subregions of A.beta. Peptide on the Inhibitory Activity of .beta.-Amyloid Modulator Compounds

Detailed Description Text (265):
These results indicate that certain subregions of A.beta..sub.1-40, when modified with an appropriate modifying group, are effective at inhibiting the aggregation of A.beta..sub.1-40. A cholyl group was an effective modifying group for several subregions. Cholic acid alone was tested for inhibitory activity but had no effect on A.beta. aggregation. The A.beta..sub.6-20 subregion exhibited high levels of inhibitory activity when modified with several different modifying groups (cholyl, NANA, iminobiotinyl), with cholyl-A.beta..sub.6-20 (PPI-264) being the most active form. Accordingly, this modulator compound was chosen for further analysis, described in Example 8.

Detailed Description Text (267):
Identification of a Five Amino Acid Subregion of A.beta. Peptide Sufficient for Inhibitory Activity of a .beta.-Amyloid Modulator Compound

Detailed Description Text (268):
To further delineate a minimal subregion of cholyl-A.beta..sub.6-20 sufficient for inhibitory activity, a series of amino terminal and carboxy terminal amino acid deletions of cholyl-A.beta..sub.6-20 were constructed. The modulators all had the same cholyl amino-terminal modification. Additionally, for the peptide series having carboxy terminal deletions, the carboxy terminus was further modified to an amide. The modulators were evaluated as described in Example 7 and the results are summarized below in Table III, wherein the data is presented as described in Example 7.

Detailed Description Text (269):
These results indicate that activity of the modulator is maintained when amino acid residue 6 is removed from the amino terminal end of the modulator (i.e., cholyl-A.beta..sub.7-20 retained activity) but activity is lost as the peptide is deleted further at the amino-terminal end by removal of amino acid position 7 through to amino acid position 12 (i.e., cholyl-A.beta..sub.8-20 through cholyl-A.beta..sub.13-20 did inhibit the plateau level of A.beta. aggregation). However, further deletion of amino acid position 13 resulted in a compound (i.e., cholyl-A.beta..sub.4-20) in which inhibitory activity is restored. Furthermore, additional deletion of amino acid position 14 (i.e., cholyl-A.beta..sub.15-20) or positions 14 and 15 (i.e., cholyl-A.beta..sub.16-20) still maintained inhibitory activity. Thus, amino terminal deletions of A.beta..sub.6-20 identified A.beta..sub.16-20 as a minimal subregion which is sufficient for inhibitory activity when appropriately modified. In contrast, carboxy terminal deletion of amino acid position 20 resulted in loss of activity which was not fully restored as the peptide was deleted further at the carboxy-terminal end. Thus, maintenance of position 20 within the modulator may be important for inhibitory activity.

Detailed Description Text (271):
Identification of a Four Amino Acid Subregion of A.beta. Peptide Sufficient for Inhibitory Activity of a .beta.-Amyloid Modulator Compound

Detailed Description Text (272):
In this example, the smallest effective modulator identified in the studies described in Example 8, cholyl-A.beta..sub.16-20 (PPI-350), was analyzed further. Additional amino- and carboxy-terminal deletions were made with cholyl-A.beta..sub.16-20, as well as an amino acid substitution (Val.sub.18 ->Thr), to identify the smallest region sufficient for the inhibitory activity of the modulator. A peptide comprised of five alanine residues, (Ala).sub.5 ; SEQ ID NO:35, modified at its amino-terminus with cholic acid, was used as a specificity control. The modulators were evaluated as described in Example 7 and the results are summarized below in Table IV, wherein the

data is presented as described in Example 7.

Detailed Description Text (273):
As shown in Table IV, cholyl-A.beta..sub.16-20 (PPI-350) and cholyl-A.beta..sub.17-21 (PPI-368) both exhibited inhibitory activity, indicating that the four-amino acid minimal subregion of positions 17-20 is sufficient for inhibitory activity. Loss of position 20 (e.g., in PPI-366 and PPI-321) resulted in loss of inhibitory activity, demonstrating the importance of position 20. Moreover, mutation of valine at position 18 to threonine (in PPI-369) also resulted in loss of activity, demonstrating the importance of position 18. In contrast, mutation of phenylalanine at position 19 to alanine (cholyl-A.beta..sub.16-20 Phe.sub.19- >Ala; PPI-370) resulted in a compound which still retained detectable inhibitory activity. Accordingly, the phenylalanine at position 19 is more amenable to substitution, preferably with another hydrophobic amino acid residue. Cholyl-penta-alanine; SEQ ID NO:35 (PPI-365) showed no inhibitory activity, demonstrating the specificity of the A.beta. peptide portion of the modulator. Moreover, unmodified A.beta..sub.16-20 (PPI-377) was not inhibitory, demonstrating the functional importance of the amino-terminal modifying group. The specific functional group influenced the activity of the modulator. For example, iminobiotinyl-A.beta..sub.16-20 (PPI-374) exhibited inhibitory activity similar to cholyl-A.beta..sub.16-20, whereas an N-acetyl neuraminic acid (NANA)-modified A.beta..sub.16-20 was not an effective inhibitory modulator (not listed in Table IV). A C-terminal amide derivative of cholyl-A.beta..sub.16-20 (PPI-319) retained high activity in delaying the lag time of aggregation, indicating that the carboxy-terminus of the modulator can be derivatized without loss of inhibitory activity. Although this amide-derivatized compound did not inhibit the overall plateau level of aggregation over time, the compound was not tested at concentrations higher than mole 33%. Higher concentrations of the amide-derivatized compound are predicted to inhibit the overall plateau level of aggregation, similar to cholyl-A.beta..sub.16-20 (PPI-350).

Detailed Description Text (283):
In this example, additional modulator compounds designed based upon amino acids 17-20 of A.beta., LVFF; SEQ ID NO:12 (identified in Example 9), were prepared and analyzed to further delineate the structural features necessary for inhibition of .beta.-amyloid aggregation. Types of compounds analyzed included ones having only three amino acid residues of an A.beta. aggregation core domain, compounds in which the amino acid residues of an A.beta. aggregation core domain were rearranged or in which amino acid substitutions had been made, compounds modified with a carboxy-terminal modifying group and compounds in which the modifying group had been derivatized. Abbreviations used in this example are: h- (free amino terminus), -oh (free carboxylic acid terminus), -nh.sub.2 (amide terminus), CA (cholyl, the acyl portion of cholic acid), NANA (N-acetyl neuraminyl), IB (iminobiotinyl), .beta.A (.beta.-alanyl), DA (D-alanyl), Adp (aminoethyldibenzofuranylpropanoic acid), Aic (3-(O-aminoethyl-iso)-cholyl, a derivative of cholic acid), IY (iodotyrosyl), o-methyl (carboxy-terminal methyl ester), N-me (N-methyl peptide bond), DeoxyCA (deoxycholyl) and LithoCA (lithocholyl).

Detailed Description Text (284):
Modulator compounds having an Aic modifying group at either the amino- or carboxy-terminus (e.g., PPI-408 and PPI-418) were synthesized using known methods (see e.g., Wess, G. et al. (1993) Tetrahedron Letters, 34:817-822; Wess, G. et al. (1992) Tetrahedron Letters 33:195-198). Briefly, 3-iso-O-(2-aminoethyl)-cholic acid (3.beta.-(2-aminoethoxy)-7.alpha.,12.alpha.-dihydroxy-5.beta.-cholanoic acid) was converted to the FMOC-protected derivative using FMOC-OSu (the hydroxysuccinimide ester of the FMOC group, which is commercially available) to obtain a reagent that was used to introduce the cholic acid derivative into the compound. For N-terminal introduction of the cholic acid moiety, the FMOC-protected reagent was coupled to the N-terminal amino acid of a solid-phase peptide in the standard manner, followed by standard FMOC-deprotection conditions and subsequent cleavage from the resin, followed by HPLC purification. For C-terminal introduction of the cholic acid moiety, the FMOC-protected reagent was attached to 2-chlorotrityl chloride resin in the standard manner. This amino acyl derivatized resin was then used in the standard manner to synthesize the complete modified peptide.

Detailed Description Text (287):
The results shown in Table V demonstrate that at an effective modulator compound can comprise as few as three A.beta. amino acids residues (see PPI-394, comprising the amino acid sequence VFF, which corresponds to A.beta..sub.18-20, and PPI-395, comprising the amino acid sequence FFA, which corresponds to A.beta..sub.19-21). The results also demonstrate that a modulator compound having a modulating group at its carboxy-terminus is effective at inhibiting A.beta. aggregation (see PPI-408, modified

at its C-terminus with Aic). Still further, the results demonstrate that the cholyl group, as a modulating group, can be manipulated while maintaining the inhibitory activity of the compounds (see PPI-408 and PPI-418, both of which comprise the cholyl derivative Aic). The free amino group of the Aic derivative of cholic acid represents a position at which a chelation group for .sup.99m Tc can be introduced, e.g., to create a diagnostic agent. Additionally, the ability to substitute iodotyrosyl for phenylalanine at position 19 or 20 of the A.beta. sequence (see PPI-396 and PPI-397) while maintaining the ability of the compound to inhibit A.beta. aggregation indicates that the compound could be labeled with radioactive iodine, e.g., to create a diagnostic agent, without loss of the inhibitory activity of the compound.

Detailed Description Text (288):
Finally, compounds with inhibitory activity were created using A.beta. derived amino acids but wherein the amino acid sequence was rearranged or had a substitution with a non-A.beta.-derived amino acid. Examples of such compounds include PPI-426, in which the sequence of A.beta..sub.17-21 (LVFFA SEQ ID NO:11) has been rearranged (FFVLA SEQ ID NO:21), PPI-372, in which the sequence of A.beta..sub.16-20 (KLVFF SEQ ID NO:10) has been rearranged (FKFVL SEQ ID NO:29), and PPI-388, -389 and -390, in which the sequence of A.beta..sub.17-21 (LVFFA SEQ ID NO:11) has been substituted at position 17, 18 or 19, respectively, with an alanine residue (AVFFA (SEQ ID NO:25) for PPI-388, LAFFA (SEQ ID NO:13) for PPI-389 and LVAFA (SEQ ID NO:33) for PPI-390). The inhibitory activity of these compounds indicate that the presence in the compound of an amino acid sequence directly corresponding to a portion of A.beta. is not essential for inhibitory activity, but rather suggests that maintenance of the hydrophobic nature of this core region, by inclusion of amino acid residues such as phenylalanine, valine, leucine, regardless of their precise order, can be sufficient for inhibition of A.beta. aggregation.

Detailed Description Text (291):
To examine the ability of unmodified A.beta. peptides to modulate aggregation of natural .beta.-AP, a series of A.beta. peptides having amino- and/or carboxy terminal deletions as compared to A.beta..sub.1-40, or having internal amino acids deleted (i.e., noncontiguous peptides), were prepared. One peptide (PPI-220) had additional, non-A.beta.-derived amino acid residues at its amino-terminus. These peptides all had a free amino group at the amino-terminus and a free carboxylic acid at the carboxy-terminus. These unmodified peptides were evaluated in assays as described in Example 7. The results are summarized below in Table VI, wherein the data is presented as described in Example 7. Compounds exhibiting at least a 1.5 fold increase in lag time are highlighted in bold.

Detailed Description Text (292):
The results shown in Table VI demonstrate that limited portions of the A.beta. sequence can have a significant inhibitory effect on natural .beta.-AP aggregation even when the peptide is not modified by a modifying group. Preferred unmodified peptides are A.beta..sub.6-20 (PPI-226), A.beta..sub.16-30 (PPI-228), A.beta..sub.1-20, 26-40 (PPI-249) and EEVVHHHHQQ-A.beta..sub.16-20 (PPI-220), the amino acid sequences of which are shown in SEQ ID NOs:4, 14, 15, and 16, respectively.

Detailed Description Paragraph Table (1):
TABLE I

Seeded In-	A.beta. Amino	Modifying	Can- didate	Effect in plate Static	Effect in shaken hibitor	Acids	Reagent	Assay	Assay*
			174	A.beta.1-15		Cholic acid	Complete ++ inhibi- tion at 100% conc		
176	A.beta.1-15	Diethylene- triamine penta acetic acid		Decreased ++		Plateau			
180	A.beta.1-15	(-)-Menthoxy acetic acid		None ++					
190	A.beta.1-15	Fluorescein carboxylic acid		Decreased ++		Plateau	(FICO)		
220	A.beta.16-40	NH.sub.2 --EVHHHHQQK- mutant [A.beta.(16-40)]-COOH		Complete ++			inhibi- tion at 100%, increased lag at 10%		
224	A.beta.1-40	F.sub.19 F.sub.20 -> T.sub.19 T.sub.20		Increased ++					
233	A6.beta.-20	Acetic acid		acceler- ++			ated aggrega- tion at 10% conc		

*++ = A strong inhibitor of aggregation. The rate of aggregation in the presence of the inhibitor was decreased compared to the control by at least 30.50%

Detailed Description Paragraph Table (5):
TABLE V

Mod.	.DELTA.Lag	%	I.sub.nucl'n	I.sub.ext'n	N-Term.	C-Term.	%	Ref. #	Mod. Peptide
PPI-293	CA	--	oh	1.0	0	ND*	PPI-315	CA	HQKLVFF
nh.sub.2	1.1	5**	ND	PPI-316	NANA	HQKLVFF			
nh.sub.2	1.5	-15	ND	PPI-319	CA	KLVFF			
nh.sub.2	5.4	70	52	PPI-339	CA	HDSGY			
nh.sub.2	1.1	-18	ND	PPI-348	CA	HQKLVFF			
oh	2.0	70**	ND	PPI-349	CA	QKLVFF			
oh	>5	100	56	PPI-350	CA	KLVFF			
oh	1.8	72	11	PPI-365	CA	AAAAA			
oh	0.8	-7	0	PPI-366	CA	QKLVF			
oh	3.1	-23	ND	PPI-368					

CA LVFFA oh >5 100 91 PPI-369 CA KLTFF oh 1.1 -16 44 PPI-370 CA KLVAF oh 2.6 73 31 PPI-371 CA KLVFF(.beta.A) oh 2.5 76 80 PPI-372 CA FKFVL oh 0.8 45 37 PPI-373 NANA KLVFF oh 0.9 16 8 PPI-374 IB KLVFF oh 1.3 86 0 PPI-375 CA KTVFF oh 1.2 18 21 PPI-377 h- KLVFF oh 1.1 0 8 PPI-379 CA LVFFAE oh 1.4 55 16 PPI-380 CA LVFF oh 1.8 72** 51 PPI-381 CA LVFF(DA) oh 2.3 56 11 PPI-382 CA LVFFA nh.sub.2 1.0 -200 91 PPI-383 h-DDIIL- VFF oh 0.4 14 0 (Adp) PPI-386 h- LVFFA oh 1.0 15 11 PPI-387 h- KLVFF nh.sub.2 1.3 -9 39 PPI-388 CA AVFFA oh 1.4 68 44 PPI-389 CA LAFFA oh 1.5 47 66 PPI-390 CA LVAFA oh 2.7 25 0 PPI-392 CA VFFA oh 2.0 76 10 PPI-393 CA LVF oh 1.3 1 0 PPI-394 CA VFF oh 1.8 55 0 PPI-395 CA FFA oh 1.0 51 6 PPI-396 CA LV(IY)FA oh >5 100 71 PPI-401 CA LVFFA o-methyl ND ND 0 PPI-405 h- LVFFA nh.sub.2 1.3 11 70 PPI-407 CA LVFFK oh >5 100** 85 PPI-408 h- LVFFA (Aic)-oh 3.5 46 3 PPI-418 h-(Aic) LVFFA oh >5 100** 87 PPI-426 CA FFVLA oh >5 100 89 PPI-391 CA LVFAA oh 1.6 40 ND PPI-397 CA LVF(IY)A oh >5 95 ND PPI-400 CA AVAFA oh 1.0 -15 ND PPI-403 *** HQKLVFF oh 1.4 -75 0 PPI-404 **** LKLVFF oh 1.8 -29 7 PPI-424 DeoxyCA LVFFA oh 3.0 -114 82 PPI-425 LithoCA LVFFA oh 2.8 -229 0 PPI-428 CA FF oh 1.7 -78 15 PPI-429 CA FFV oh 2.2 -33 7 PPI-430 CA FFVL oh 4.1 33 75 PPI-433 CA LVFFA oh 2.8 27 ND (all D amino acids) PPI-435 t-Boc LVFFA oh 3.0 -5 ND PPI-438 CA GFF oh 1.0 0 ND

*ND = not done **33 mol %

***hDDIII(N-Me-Val)DLL(Adp) ****hDDII(N-Me-Leu)VEH(Adp)

Detailed Description Paragraph Table (7):

SEQ ID NO: Amino Acids Peptide Sequence

1 43 amino acids A.beta..sub.1-43 2 103 amino acids APP C-terminus 3 43 amino acids A.beta..sub.1-43 (19, 20 mutated) 4 HDSGYEVHHQKLVFF A.beta..sub.6-20 5 HQKLVFFA A.beta..sub.14-21 6 HQKLVFF A.beta..sub.14-20 7 QKLVFFA A.beta..sub.15-21 8 QKLVFF A.beta..sub.15-20 9 KLVFFA A.beta..sub.16-21 10 KLVFF A.beta.16-20 11 LVFFA A.beta..sub.17-21 12 LVFF A.beta..sub.17-20 13 LAFFA A.beta..sub.17-21 (V.sub.18 .fwdarw.A) 14 KLVFFAEDVGSNKGA A.beta..sub.16-30 15 35 amino acids A.beta..sub.1-20, 26-40 16 35 amino acids EEVVHHHHQQ-.beta.AP.sub.16-40 17 AGAAAAGA PrP peptide 18 AILSS amylin peptide 19 VFF A.beta..sub.18-20 20 FFA A.beta..sub.19-21 21 FFVLA A.beta..sub.17-21 (scrambled) 22 LVFFK A.beta..sub.17-21 (A.sub.21 .fwdarw.K) 23 LV(IY)FA A.beta..sub.17-21 (F.sub.19 .fwdarw.IY) 24 VFFA A.beta..sub.18-21 25 AVFFA A.beta..sub.17-21 (L.sub.17 .fwdarw.A) 26 LVF(IY)A A.beta..sub.17-21 (F.sub.20 .fwdarw.IY) 27 LVFFAE A.beta..sub.17-22 28 FFVL A.beta..sub.17-20 (scrambled) 29 FKFVL A.beta..sub.16-20 (scrambled) 30 KLVAF A.beta..sub.16-20 (F.sub.19 .fwdarw.A) 31 KLVFF(.beta.A) A.beta..sub.16-21 (A.sub.21 .fwdarw..beta.A) 32 LVFF(DA) A.beta..sub.17-21 (A.sub.21 .fwdarw.DA)

Detailed Description Paragraph Table (8):

SEQUENCE LISTING (1) GENERAL INFORMATION: (iii) NUMBER OF SEQUENCES: 40 (2) INFORMATION FOR SEQ ID NO:1: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 43 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1: AspAlaGluPheArgHisAspSerGlyTyrGluValHisHisGlnLys 151015 LeuValPhePheAlaGluAspValGlySerAsnLysGlyAlaIleIle 202530 GlyLeuMetValGlyGlyValValIleAlaThr 3540 (2) INFORMATION FOR SEQ ID NO:2: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 103 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2: GluValLysMetAspAlaGluPheArgHisAspSerGlyTyrGluVal 151015 HisHisGlnLysLeuValPhePheAlaGluAspValGlySerAsnLys 202530 GlyAlaIleIleGlyLeuMetValGlyGlyValValIleAlaThrVal 354045 IleValIleThrLeuValMetLeuLysLysLysGlnTyrThrSerIle 505560 HisHisGlyValValGluValAspAlaAlaValThrProGluGluArg 65707580 HisLeuSerLysMetGlnGlnAsnGlyTyrGluAsnProThrTyrLys 859095 PhePheGluGlnMetGlnAsn 100 (2) INFORMATION FOR SEQ ID NO:3: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 43 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (ix) FEATURE: (A) NAME/KEY: Modified site (B) LOCATION: 19 (D) OTHER INFORMATION: /note= Xaa is a hydrophobic amino acid (ix) FEATURE: (A) NAME/KEY: Modified site (B) LOCATION: 20 (D) OTHER INFORMATION: /note= Xaa is a hydrophobic amino acid (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3: AspAlaGluPheArgHisAspSerGlyTyrGluValHisHisGlnLys 151015 LeuValXaaXaaAlaGluAspValGlySerAsnLysGlyAlaIleIle 202530 GlyLeuMetValGlyGlyValValIleAlaThr 3540 (2) INFORMATION FOR SEQ ID NO:4: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 15 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4: HisAspSerGlyTyrGluValHisHisGlnLysLeuValPhePhe 51015 (2) INFORMATION FOR SEQ ID NO:5: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 8 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:5: HisGlnLysLeuValPhePheAla (2) INFORMATION FOR SEQ ID NO:6: (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 7 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:6: HisGlnLysLeuValPhePhe 5 (2) INFORMATION FOR SEQ ID NO:7: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 7 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7: GlnLysLeuValPhePheAla 5 (2) INFORMATION FOR SEQ ID NO:8: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 6 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:8: GlnLysLeuValPhePhe 5 (2) INFORMATION FOR SEQ ID NO:9: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 6 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:9: LysLeuValPhePheAla 5 (2) INFORMATION FOR SEQ ID NO:10: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 5 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:10: LysLeuValPhePhe 5 (2) INFORMATION FOR SEQ ID NO:11: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 5 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:11: LeuValPhePheAla 5 (2) INFORMATION FOR SEQ ID NO:12: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 4 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:12: LeuValPhePhe (2) INFORMATION FOR SEQ ID NO:13: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 5 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:13: LeuAlaPhePheAla 15 (2) INFORMATION FOR SEQ ID NO:14: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 15 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:14: LysLeuValPhePheAlaGluAspValGlySerAsnLysGlyAla 151015 (2) INFORMATION FOR SEQ ID NO:15: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 35 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:15: AspAlaGluPheArgHisAspSerGlyTyrGluValHisHisGlnLys 151015 LeuValPhePheSerAsnLysGlyAlaIleIleGlyLeuMetValGly 202530 GlyValVal 35 (2) INFORMATION FOR SEQ ID NO:16: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 35 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:16: GluGluValValHisHisHisHisGlnGlnLysLeuValPhePheAla 151015 GluAspValGlySerAsnLysGlyAlaIleIleGlyLeuMetValGly 202530 GlyValVal 35 (2) INFORMATION FOR SEQ ID NO:17: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 8 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:17: AlaGlyAlaAlaAlaAlaGlyAla 15 (2) INFORMATION FOR SEQ ID NO:18: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 5 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:18: AlaIleLeuSerSer 15 (2) INFORMATION FOR SEQ ID NO:19: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 3 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:19: ValPhePhe 1 (2) INFORMATION FOR SEQ ID NO:20: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 3 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:20: PhePheAla 1 (2) INFORMATION FOR SEQ ID NO:21: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 5 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:21: PhePheValLeuAla 15 (2) INFORMATION FOR SEQ ID NO:22: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 5 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:22: LeuValPhePheLys 15 (2) INFORMATION FOR SEQ ID NO:23: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 5 amino acids (B) TYPE: amino acid

Detailed Description Paragraph Table (9):
(D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (ix) FEATURE: (A) NAME/KEY: Modified site (B) LOCATION: 3 (D) OTHER INFORMATION: /note= Xaa is iodotyrosyl (xi) SEQUENCE DESCRIPTION: SEQ ID NO:23: LeuValXaaPheAla 15 (2) INFORMATION FOR SEQ ID NO:24: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 4 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:24: ValPhePheAla 1 (2) INFORMATION FOR SEQ ID NO:25: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 5 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:25: AlaValPhePheAla 15 (2) INFORMATION FOR SEQ ID NO:26: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 5 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (ix) FEATURE: (A) NAME/KEY: Modified site (B) LOCATION: 4 (D) OTHER INFORMATION: /note= Xaa is iodotyrosyl (xi) SEQUENCE DESCRIPTION: SEQ ID NO:26: LeuValPheXaaAla 1 (2) INFORMATION FOR SEQ ID NO:27: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 6 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: peptide (xi) SEQUENCE DESCRIPTION: SEQ ID NO:27: LeuValPhePheAlaGlu 15 (2) INFORMATION FOR SEQ ID NO:28: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 4 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: